REMARKS

Attached hereto is a marked-up version of the changes made to the Specification by the current amendment. The attached page is captioned "Version with markings to show changes made."

Status of the Claims

Claims 1-10, 12-29, 46 and 47 have been canceled.

Claims 11 and 30-45 are currently pending.

Claims 1, 11 and 30-45 were subject to a Restriction Requirement. Applicants affirm election, with traverse, of claims 11, 31-32, 34, and 36-43, corresponding to the invention of Group II, antibodies which ***specifically bind*** to polypeptides of SEQ ID NO:1, compositions comprising the antibodies and methods of making the antibodies.

The examination of claims 30, 33, 35 and 44-45 is held in abeyance pending determination of allowability of any of the product claims from which they depend.

Amendment to the Title

As suggested by the Examiner, the title of the invention has been amended to be more descriptive of the claimed invention. The title as amended reads, "ANTIBODIES TO A HUMAN PHOSPHATIDYLINOSITOL 4,5-BISPHOSPHATE 5-PHOSPHATASE."

Submission of a Substitute Sequence Listing

Applicants are hereby submitting a substitute copy of the Sequence Listing, a CRF thereof and the statement of the sameness of the Sequence Listing and CRF under separate cover. The Sequence Listing is being corrected to accurately depict the sequence described as SEQ ID NO:3 (GI 1399105). Page 4 of the instant Specification describes Figures 2A-2E as containing SEQ ID NO:3, identified by GI 1399105, which is indeed the 397 amino acid residue sequence of GI 1399105 displayed in the sequences aligned in Figures 2A-2E. A similar description of SEQ ID NO:3 is found on page 13, lines 20-24 of the Specification. The Examiner correctly brought to Applicants' attention that SEQ ID NO:3 of the Sequence Listing is set forth as GI 1399101. Support for this correction to the Sequence

Listing can be found in Figures 2A-2E. Accordingly, there is no new matter in the Substitute Sequence Lisiting.

Amendments to the Specification

Applicants have amended the "Summary of the Invention" section of the Specification to include recitation of claims 36 and 39 as amended (*infra*). The two paragraphs inserted into the Specification beginning on page 3, line 22 recite subject matter present in the invention as filed. Therefore, the addition of these two paragraphs does not constitute new matter.

The requested amendments to the Specification correct clerical errors in the Specification. Justifications for the amendments to the Specification are as follows. On page 4 of the Specification Figure 2 is described as consisting of Figures 2A-2E. The paragraph beginning on page 13, line 17 of the Specification describes Figure 2 as "Figures 2A-F" (page 13, line 20). Applicants have amended the paragraph beginning on page 13, line 17 to correctly describe the contents of Figure 2 to now read, "Figures 2A-E." In support of this amendment Applicants cite the contents of the Specification as filed on the Post card enclosed with the instant Application, in which Figure 2 is listed as "2A, 2B, 2C, 2D, 2E." Thus, the Post card confirms that Figure 2 consists of Figures 2A, 2B, 2C, 2D, and 2E.

The paragraph found on page 50, starting at line 15 has been amended to correct that the amino acid sequence is "deduced from SEQ ID NO:1." The paragraph had listed the amino acid sequence as SEQ ID NO:2, which is the polynucleotide sequence encoding SEQ ID NO:1 as is presented in the Sequence Listing.

Therefore, Applicants believe the requested amendments to the specification are proper.

Objections and Amendments to the Claims

Claims 11, 34, 36 and 39 have been amended.

Claim 34 was objected to by the Examiner.

Claim 11 has been amend to remove recitation of 90% variants and immunogenic fragments of SEQ ID NO:1. Claim 11 has also been amended to recite, "an isolated human antibody . . ." (emphasis added). Support for this amendment can be found on page 2, lines 14-17 of the

Specification. Claim 11 as amended recites, "[a]n isolated human antibody which specifically binds to a polypeptide consisting of a polypeptide comprising the amino acid sequence of SEQ ID NO:1."

Claim 34 was objected to for failing to further limit the antibody in the composition of claim 32. Claim 34 has been amend to further limit claim 32, from which it depends. Claim 34 now recites, "[a] composition of claim 32, further comprising a label." Support for this amendment can be found throughout the Specification, see for example, page 35, lines 5-13; pages 23-24.

Claims 36 and 39 were amended to remove recitation of "immunogenic fragments" of SEQ ID NO:1. Additionally, while not acquiescing to the Examiner's position, Applicants have amended the claims to remove procedural steps self-evident to the skilled artisan. Applicants assert that these amendments were done in order to expedite prosecution of the subject application. Applicants expressly do not disclaim equivalents which could include: variants and immunogenic fragments of SEQ ID NO:1, isolating polyclonal or monoclonal human antibodies which specifically bind to a polypeptide consisting of a polypeptide comprising the amino acid sequence of SEQ ID NO:1 or fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells.

Objections to the Specification

The Specification was objected to for an alleged lack of "clear antecedent basis for each of the method steps of claims 36 and 39; and therefore the products of claims 37-38 and 40-41." The Office has requested Applicants to "identify support in the instant specification for each method step, particularly step "b" of claim 36 and steps "b," "c" and "e" of claim 39" (Office Action of December 16, 2002, page 3, § 9).

Please note that claims 36 and 39 have been amended and these amended claims clearly have antecedent basis in the Specification as filed (see for example, Example XI, page 50, methods of producing polyclonal antibodies and for example, see pages 27-28 of the Specification, methods of producing monoclonal antibodies). In addition, in the interest of expediting prosecution and not for reasons related to patentability, Applicants have amended the Specification to include a narrative summary of claims 36 and 39 as now amended. No new matter was added by the amendment.

Applicants also assert that the courts have ruled that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. V. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. The MPEP at 2163 II. A. 3.(a) states, "[i]f the skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116." Accordingly, the actual methods of producing the monoclonal and polyclonal antibodies are well known to those skilled in the art and are considered by the courts to be routine. Therefore, amending the Specification to include steps involved in these methods of production would not be considered new matter as well as the fact that Applicants have incorporated by reference references which provide the claimed methods.

Additionally, the Specification teaches and Applicants assert that one of ordinary skill in the art would also be able to isolate polyclonal and monoclonal antibodies by reverse engineering Example XII, page 51 of the Specification. Example XII teaches methods to purify SEQ ID NO:1 using antibodies. Just as Example XII teaches the attachment of antibodies specific for SEQ ID NO:1 to an immunoaffinity column, so to could SEQ ID NO:1 be attached to a protein binding affinity column, and then antibodies for SEQ ID NO:1 passed over the column and then eluted and collected (i.e., isolated).

Rejection under 35 U.S.C. § 112, first paragraph, Enablement

Claims 11, 31-32, 34 and 36-43 have been rejected under 35 U.S.C. § 112, first paragraph, "because the specification, while being enabling for antibodies or fragments thereof which specifically bind SEQ ID NO:1 or immunogenic fragments thereof, does not reasonably provide enablement for antibodies or fragments thereof which specifically bind an isolated polypeptide comprising various naturally occurring "variants" of SEQ ID NO:1, as set forth in instant claim 11b (emphasis added)." (Office Action of December 16, 2002, page 4, § 12). Applicants traverse this rejection.

Without acquiescing to the reason for this rejection, claim 11 has been amended to remove recitation of, "a naturally occurring amino acid sequence at least 90% identical to the amino acid

sequence of SEQ ID NO:1. Therefore, rejection of claim 11 and the claims that depend from it, either directly or indirectly, claims 31-32, 34, 36-43 is rendered moot by the amendments to claim 11 concerning antibodies to variants of the polypeptide of SEQ ID NO:1. Withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a), Obviousness

Each of the prior art rejections under 35 U.S.C. § 103(a) is based upon the combination of GenBank Accession No. AAB03214 (GI 1399101, Nussbaum, R.L.) with other references including: 1) Laxminarayan et al., (J. Biol. Chem. 1993; 268:4968-4974); 2) Palmer et al., (J. Biol. Chem. 1994; 269:3404-3410), and 3) Ramakrishnan et al. (U.S. Pat. No. 5,817,310). In particular, claims 11, 32, 34 and 36-38 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Laxminarayan et al. in view of GenBank Accession No. AAB03214; claims 11, 32, 34 and 39-41 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Palmer et al. in view of GenBank Accession No. AAB03214 and claims 31 and 42-43 stand rejected under 35 U.S.C. § 103(a) for allegedly being "unpatentable over Palmer et al., in view of GenBank Accession No. AAB03214," and further in view of Ramakrishnan et al. These rejections therefore are respectfully traversed.

While not acquiescing the propriety of the Patent Office position, claim 11 has been amended to delete recitation of an amino acid sequence at least 90% identical to SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity and the immunogenic fragments of SEQ ID NO:1. Further, claim 11 has been amended to include the recitation of **human** to more clearly identify that which Applicants have claimed as their invention.

The claimed invention, as amended, is directed to an isolated ***human*** antibody which ***specifically binds*** to a polypeptide consisting of a polypeptide comprising the amino acid sequence of SEQ ID NO:1 and compositions comprising and methods directed to making and using said antibodies. By **"specifically binding"** to SEQ ID NO:1, the antibody can bind to a polypeptide consisting of SEQ ID NO:1 without cross-reactivity to other polypeptides even those which have extensive sequence identity to SEQ ID NO:1. Accordingly, so long as there are differences, even just one amino

acid residue, between the claimed sequence and those of the prior art, an antibody can be produced that can specifically bind to the claimed polypeptide and not those of the prior art.

Even the Examiner recognizes this fact. The Examiner has relied previous on the Abaza et al. reference (J. Protein Chem. (1992) 11:433-444, of record). As taught by Abaza et al., a single amino acid substitution outside the antigenic site on a protein effect antibody binding. This provides scientific support of Applicants' assertion that so long as there are differences, even just one amino acid residue, between the claimed sequence and those of the prior art, an antibody can be produced that can specifically bind to the claimed polypeptide and not those of the prior art. Accordingly, given the amino acid differences between SEQ ID NO:1 and GenBank Accession No. AAB03214, one of skill in the art could produce an antibody to SEQ ID NO:1 which binds to the claimed polypeptide alone and without cross-reactivity to other polypeptides even those which have extensive sequence identity to SEQ ID NO:1.

As stated above, GenBank Accession No. AAB03214 lacks amino acid residues 1-44 of SEQ ID NO:1. Moreover, in the alignment provided by the Examiner, there are two residues within SEQ ID NO:1, S340 and S350, which differ from GenBank Accession No. AAB03214. Neither Laxminarayan et al., nor Palmer et al. overcome the deficiencies of GenBank Accession No. AAB03214. Furthermore, Palmer et al. actually teach ***bovine*** antibodies and not **human** antibodies and therefore in view of GenBank Accession No. AAB03214, actually teaches away from the claimed invention. Hence, the cited art of GenBank Accession No. AAB03214, Palmer et al., Laxminarayan et al., and Ramakrishnan et al. could not have guided one of ordinary skill in the art to the claimed **human** antibodies which **specifically bind** to SEQ ID NO:1. For at least the above reasons, Applicants believe withdrawal of the § 103 rejections are appropriate and are hereby requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE TITLE

[NEW] ANTIBODIES TO A HUMAN PHOSPHATIDYLINOSITOL 4,5-BISPHOSPHATE 5-PHOSPHATE

IN THE SPECIFICATION:

The following two paragraphs have been inserted into the Specification beginning at line 22 of page 3:

The invention also provides a method of preparing a polyclonal antibody with the specificity of the an isolated human antibody which specifically binds to a polypeptide consisting of a polypeptide comprising the amino acid sequence of SEQ ID NO:1, comprising immunizing an animal with a polypeptide having an amino acid sequence of SEQ ID NO:1, under conditions to elicit an antibody response and screening for a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO:1.

The invention further provides a method of making a monoclonal antibody with the specificity of an isolated human antibody which specifically binds to a polypeptide consisting of a polypeptide comprising the amino acid sequence of SEQ ID NO:1, comprising immunizing an animal with a polypeptide having an amino acid sequence of SEQ ID NO:1, under conditions to elicit an antibody response screening for a monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO:1.

The paragraph beginning at line 17 of page 13 to line 3 of page 14 has been amended as follows:

In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:1, as shown in Figures 1A-G. PBPP is 372 amino acids in length and has potential phosphorylation sites at S38, S132, T170, S183, T192, S275, S282, R295, S312, T329, T330, and S359. As shown in Figures [2A-F] 2A-E, PBPP has chemical and structural homology

with a partial human phosphatidylinositol 4,5-bisphosphate 5-phosphatase (GI 1399105; SEQ ID NO:3), an inositol polyphosphate 5 phosphatase (GI 1019103; SEQ ID NO:4), and Lowe's oculocerebrorenal syndrome protein (GI 1420920; SEQ ID NO:5). Two potential catalysis or binding sites conserved among these related molecules are N104-D123 and D181-K200. PBPP has 124 unique residues 5' of the published sequence for the partial human phosphatidylinositol 4,5-bisphosphate 5-phosphatase; beyond residue F124, they share 64% identity. The lack of an isoprenylation motif suggests that PBPP is a cytosolic enzyme. Northern analysis shows the expression of this sequence in various libraries, at least 31% of which are associated with inflammation or immune disorders, at least 26% are from immortalized or cancerous cells or tissues, at least 11% of are from fetal or infant tissues and at least 11% of which involve tissues of the neuronal tissues (Figures 3A-C) Of particular note is the association of PBPP with libraries undergoing or associated with cell proliferation.

The paragraph beginning at line 15, page 50 has been amended as follows:

PBPP that is substantially purified using PAGE electrophoresis (Sambrook, supra), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols. The amino acid sequence deduced from [SEQ ID NO:2] SEQ ID NO:1 is analyzed using DNASTAR software (DNASTAR Inc.) to determine regions of high immunogenicity and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions, is described by Ausubel et al. (supra), and others.

IN THE CLAIMS:

Claims 11, 34, 36 and 39 have been amended as follows:

11. (**Twice** Amended) An isolated human antibody which specifically binds to a polypeptide [selected from the group consisting of:

a)] consisting of a polypeptide comprising the amino acid sequence of SEQ ID NO:1[,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity, and

c) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1].

34. **(Once Amended)** A composition of claim 32, further comprising a label **[**wherein the antibody is labeled**]**.

36. (**Twice** Amended) A method of preparing a polyclonal antibody with the specificity of the antibody of claim 11, the method comprising:

a) immunizing an animal with a polypeptide having an amino acid sequence of SEQ ID NO:1 [or an immunogenic fragment thereof,] under conditions to elicit an antibody response; and

b) [isolating antibodies from said animal; and

c)] screening for [the isolated antibodies with the polypeptide, thereby identifying] a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO:1.

39. (**Twice** Amended) A method of making a monoclonal antibody with the specificity of the antibody of claim 11, the method comprising:

a) immunizing an animal with a polypeptide having an amino acid sequence of SEQ ID NO:1 [or an immunogenic fragment thereof,] under conditions to elicit an antibody response; and

b) [isolating antibody producing cells from the animal;

c) producing a hybridoma continuous cell line which produces a monoclonal antibody to SEQ ID NO:1 fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells;

d) culturing the hybridoma cells;] and

[e) isolating from

f)] screening [the culture] for a monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO:1.